FORM PTO-1390 (Rev. 1-98) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE ATTORNEY'S DOCKET NUMBER JAB 120

PCT

# TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371



U S APPLICATION NO (If known, see 37 CFR 1.5)

09/403056

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/EP98/02143 | April 7, 1998 | April 14, 1997 |

TITLE OF INVENTION

COMPOSITIONS CONTAINING AN ANTIFUNGAL AND A PHOSPHOLIPID

APPLICANT(S) FOR DO/EO/US :

Embrechts et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).

9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information:

| U.S. APPLICATION NO (if known, see 37 CFR 1 5) | INTERNATIONAL APPLICATION NO | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 09/403056 | PCT/EP98/02143 | JAB-1267 |

17. ☒ The following fees are submitted:

| BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)): | CALCULATIONS PTO USE ONLY |
|---|---|
| Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO..... ..... $1070.00 | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....$930.00 | |
| International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.455(a)(2)) paid to USPTO..... $790.00 | |
| International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... $720.00 | |
| International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)..... $98.00 | |
| ENTER APPROPRIATE BASIC FEE AMOUNT = | $ 930.00 |
| Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $ |

| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
|---|---|---|---|---|---|
| Total claims | 14 - 20 = | 0 | x $22.00 | $0 | |
| Independent claims | 1 - 20 = | 0 | x $82.00 | $0 | |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | + $270.00 | $0 | |
| TOTAL OF ABOVE CALCULATIONS = | | | | $930.00 | |
| Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). | | | + | $ | |
| SUBTOTAL = | | | | $930.00 | |
| Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) . | | | | $ | |
| TOTAL NATIONAL FEE = | | | | $930.00 | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property + | | | | $40.00 | |
| TOTAL FEES ENCLOSED = | | | | $970.00 | |
| | | | | Amount to be refunded: | $ |
| | | | | charged: | $970.00 |

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 10-0750/JAB-1267/MAA in the amount of $970.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 10-0750/JAB-1267/MAA. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

Audley A. Ciamporcero, Jr., Esq.
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Mary A. Appollina
Signature

Mary A. Appollina
Reg. No. 34,087
Attorney for Applicants

DOCKET NO. JAB-1267

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Embrechts et al

For : COMPOSITIONS CONTAINING AN ANTIFUNGAL AND A PHOSPHOLIPID

Express Mail Certificate

"Express Mail" mailing number: EL327258159US

Date of Deposit: October 13, 1999

I hereby certify that this complete application, including specification pages, claims, Information Disclosure Statement, Declaration and Power of Attorney, and Assignment, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Melissa A. Smith
(Typed or printed name of person mailing paper or fee)

Melissa A Smith
(Signature of person mailing paper or fee)

Docket No. JAB-1267

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants : Embrechts et al

Serial No. : Art Unit:

Filed : Examiner:

For : COMPOSITIONS CONTAINING AN ANTIFUNGAL AND A PHOSPHOLIPID

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

October 13, 1999

(Date)

Mary A. Appollina

Name of applicant, assignee, or Registered Representative

Mary A. Appollina

(Signature)

October 13, 1999

(Date of Signature)

Assistant Commissioner for Patents
Washington, D.C. 20231

**PRELIMINARY AMENDMENT**

Dear Sir:

Please amend the above-identified application as follows and consider the following remarks.

In the Specification

On page 1, between the title and line 5, add the following new paragraph:

-- Cross Reference to Related Applications.

This application is a National Stage application under 35 U.S.C.371 of PCT/EP98/02143 filed April 7, 1998, which claims priority from EP 97.201.101.9, filed April 14, 1997. --

In the Claims:

In claim 4, line 1, replace "claim 1, 2 or 3" with --claim 1--.

In claim 5, line 1, replace "any one of the preceding claims" with --claim 1--.

In Claim 6, line 1, replace "any one of the preceding claims" with --claim 1--.

In Claim 14, line 7, replace "any one of the preceding claims" with --claim 7--.

**REMARKS**

The specification has been amended to refer to the priority applications.

The claims have been amended to remove the use of multiple dependent claims.

Early favorable action is respectfully requested.

Respectfully submitted,

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Dated: October 13, 1999

# COMPOSITIONS CONTAINING AN ANTIFUNGAL AND A PHOSPHOLIPID

The invention relates to compositions such as body and hair cleansing products, in particular shampoos, comprising one or more antifungals inhibiting fungal ergosterol biosynthesis as a first active ingredient, a synthetic, amphotheric phospholipid acting both as a second active ingredient and as a surface active agent, and art-known body or hair cleansing product ingredients as a carrier.

## Background of the invention

Known medicated shampoos are, for example, the ketoconazole shampoos which are marketed in a 2 % formulation and which show a beneficial effect in dandruff and seborrheic dermatitis after topical application. Ketoconazole was disclosed by Rosenberg et al. in US-4,569,935 to be useful in the topical treatment of psoriasis and seborrheic dermatitis. Ketoconazole shampoos that exhibit better cosmetic attributes such as lathering and conditioning, and are acceptably stable to degradation so that they can be formulated to contain less than 2 % active ingredient are disclosed in US-5,456,851. Elubiol shampoos having a skin grease regulating action are known from WO-93/18743. Some anti-dandruff formulations contain coal tar, selenium sulfide or a pyrithione salt, e.g. zinc or sodium pyrithione as an active agent. WO-96/29045 generically discloses combinations of such a cytotoxic agent and an antifungal agent for the treament of seborrheic dermatitis of the scalp ; specifically disclosed is the combined use of an unidentified composition comprising 1.8 % coal tar and an unidentified solution comprising 2 % ketoconazole. WO-96/29983 discloses mild aqueous detergent compositions comprising from about 4 to about 12 % by weight of an anionic surfactant, an amphoteric surfactant at a level of at least about 0.75 parts by weight per part by weight of said anionic surfactant, and one or more of 11 listed therapeutic agents.

US-4,209,449 (EP-0,013,713) discloses synthetic, amphotheric phospholipids which exhibit outstanding foaming, viscosity-building, wetting, cleansing, detergency, anti-static and emulsifying properties. A number of the synthetic, amphotheric phospholipids described therein are commercially available from Mona Industries, Inc., Paterson, NJ, USA under the name Phospholipid PTC (cocamidopropyl phosphatidyl PG-dimonium chloride), Phospholipid EFA (linoleamidopropyl phosphatidyl PG-dimonium chloride), Phospholipid PTS (stearamidopropyl phosphatidyl PG-dimonium chloride).

Prior art shampoos comprising anti-dandruff agents are designed in such a way that an optimum balance is achieved between efficacy and tolerability ; the concentration of the active ingredient in the medicated shampoos is such that as many users as possible are effectively treated and as few as possible suffer adverse effects. Nonetheless, there remain substantial numbers of patients who do not benefit from using prior art shampoos, either because they do not respond to the treatment, or worse, because they do not tolerate the treatment with a particular medicated shampoo.

The number of patients not responding to particular medicated shampoo can be quite high (ketoconazole up to 30 % ; selenium sulfide up to 40 %). Consequently, there is a hard felt need for new shampoos which provide effective anti-dandruff treatment for a larger proportion of number of patients using such a new shampoo ; i.e. a new shampoo for which there are fewer non-respondents than with prior art shampoos.

On the other hand, patients suffering from dandruff or seborrheic dermatitis, as well as the authorities approving medicated shampoos, apply increasingly stricter criteria which such shampoos should meet. Amongst these criteria the most important are : absence of further aggravation of the condition due to the treatment, lowest possible incidence of side effects, further increase in the absence of symptoms such as irritation, pruritus and scaling (both adherent and loose scaling) ; improved cosmetic acceptability, in particular, good cleansing properties, absence of odour or stench, absence of staining or soiling of the clothes, and overall conditioning (wet and dry combing properties). Dandruff or seborrheic dermatitis are often accompanied by high or excessive oil or sebum production, and compositions having a beneficial effect thereon would clearly constitute a further advance in the treatment of dandruff.

Thus far, in order to achieve the above desiderata, most efforts have involved reformulating the shampoo base. There is, however, still a need for increasing the tolerability / acceptability of medicated shampoos, i.e. new shampoos are desired that are tolerated better by larger proportions of patients using such new shampoos.

Description of the invention

The present invention relates to compositions such as body and hair cleansing products, in particular shampoos, comprising, consisting essentially of or consisting of one or more antifungals inhibiting fungal ergosterol biosynthesis as a first active ingredient, a synthetic, amphotheric phospholipid as a second active ingredient, and art-known body

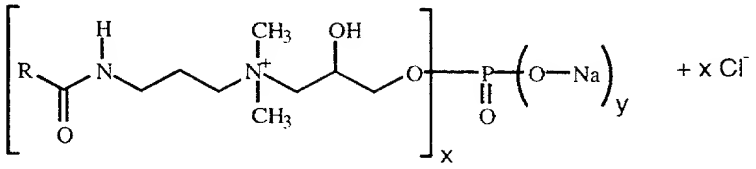
and hair cleansing product ingredients as a carrier. In the following description, the invention is illustrated using shampoos as examples, but it will be evident to a person skilled in the art that the combinations according to the present invention can be utilized just as well in other body and hair cleansing products.

The combination of two differently acting anti-dandruff agents has two distinct advantages over the prior art shampoos which contain either of the active ingredients alone. First, an increased proportion of patients suffering from dandruff or seborrheic dermatitis respond to the shampoos according to the present invention. Secondly, some combinations act synergistically and as a consequence thereof, the concentration of one or both of the different types of agent can be lowered, thus increasing the tolerability. Each class of ingredients will now be discussed in turn.

Many of the ingredients discussed hereinafter are commercially available in formulations (e.g. aqueous solutions), not as pure compounds. The amount of ingredient which can be used in preparing formulations according to the present invention are usually expressed as % (w/w) and refer to the amount of the commercially available product to be used, not the amount of pure product.

The antifungal inhibiting fungal ergosterol biosynthesis is preferably an azole, an allylamine, or a mixture thereof. Preferred azoles are selected from the group comprising ketoconazole, econazole, elubiol, miconazole, itraconazole, fluconazole and mixtures thereof. Preferred allylamines are selected from the group comprising terbinafine, naftifine and mixtures thereof. The azole compounds ketoconazole, econazole and elubiol are most preferred because they harm the normal flora of the skin, in particular of the scalp, the least. Ketoconazole and elubiol are especially preferred as they produce a mutual synergistic effect on dermatophyte fungi when in used in combination with a phospholipid (vide infra). Effective amounts of the antifungals in compositions according to the present invention are in the range of from about 0.1 % to about 2 % (w/w), and preferably from about 0.5 % to about 1 % (w/w). As will be explained further, at the lower end of this range, special precautions may have to be taken in order to ensure that the shampoo does not lose its efficacy due to degradation of the antifungal compound upon storage. Concentrations higher than those indicated do not improve the treatment of the conditions any further, and are on the whole more detrimental than beneficial.

The second active ingredient is a synthetic, amphotheric phospholipid having the formula



wherein R represents a straight, saturated, mono-unsaturated or poly-unsaturated C7-19 alkyl group ; x represents 1, 2 or 3 and x + y = 3 ; and mixtures thereof. The radical R-(C=O)- thus represents the acyl residue of a straight, saturated, mono-unsaturated or poly-unsaturated C8-20 carboxylic acid ; examples of such acids are octanoic (caprylic), nonanoic, decanoic (capric), undecanoic, 10-undecenoic, dodecanoic (lauric), tridecanoic, tetradecanoic (myristic), pentadecanoic, hexadecanoic (palmitic), palmitoleic, heptadecanoic, octadecanoic (stearic), 9-octadecenoic (oleic), 9,12-octadecadienoic (linoleic), 9,12,15-octadecatrienoic (linolenic), nonadecanoic, eicosanoic (arachidic) and 5,8,11,14-eicosatetraenoic (arachidonic) acid. The phospholipids may be present in an amount ranging from about 0.04 % to about 10 % (w/w), and preferably from about 0.25 % to about 2 % (w/w). One skilled in the art will readily recognize that the nature of the particular phospholipid form has an effect on the amount when expressed as % (w/w). Preferred phospholipids are those wherein R-(C=O)- represents the acyl residue of stearic, linoleic or coconut fatty acid (which is a mixture of lauric, myristic, palmitic and stearic acids). The phospholipids and their preparation are known from US-4,209,449. Some are commercially available from the assignee of said patent, Mona Industries, Inc, Paterson, New Jersey, USA : e.g. Phospholipid PTC (cocamidopropyl phosphatidyl PG-dimonium chloride), Phospholipid EFA (linoleamidopropyl phosphatidyl PG-dimonium chloride), Phospholipid SV (palmitamidopropyl phosphatidyl PG-dimonium chloride), and Phospholipid PTS (stearamidopropyl phosphatidyl PG-dimonium chloride).

Phospholipid PTC is the most preferred second active ingredient and is an aqueous formulation having a solid contents of 47 %, appearing as a clear yellow liquid and giving a pH of about 7 when diluted to 10 % in 50/50 2-propanol/water.

Preferably, the first and the second active ingredients are present in quantities producing a mutual synergistic effect on the inhibition of the growth of dermatophyte fungi, in particular the species associated with dandruff and seborrheic dermatitis, i.e. Malassezia furfur (Pityrosporum ovale), but also other fungi such as Epidermophyton, Microsporum, Trichophyton species associated with, for example, dermatophytosis.

pityriasis versicolor and the like. The ratio of the quantities of the first and the second active ingredient will depend on the nature of said active ingredients and on the target species. Particularly, it is contemplated that the weight : weight ratio between the first and the second active ingredient (antifungal : pyrithione) may range from about 5 : 1 to about 1 : 150, in particular from about 2 : 1 to about 1 : 25. For example, and as already mentioned, ketoconazole and elubiol when in used in combination with a phospholipid, in particular when used in similar quantities such as in a weight ratio ranging from about 2 : 1 to about 1 : 25, in particular in a weight range of about 1 : 20, produce a mutual synergistic effect on fungi, in particular on Malassezia furfur.

The shampoos according to the present invention can conveniently be formulated using art-known shampoo bases ; the art-known shampoo ingredients comprise one or more of a surfactant, a foaming agent, a thickener, a preservative, an anti-oxidant, and acid or base or buffer sufficient to give the shampoo a pH in the range of from about 4 to about 10. A single ingredient can have two or more functions, e.g. surfactant and foaming agent, or anti-oxidant and buffer.

Suitable surfactants for use in the shampoos according to the present invention may be selected from the group comprising sodium C14-16 olefin sulfonates, sodium lauryl sulfate, TEA lauryl sulfate, sodium laureth sulfate, cocamidopropylamine oxide, lauryl amine oxide, lauramido DEA, cocamidopropyl betaine, lauryl dimethyl betaine, cocodimethyl sulfo-propyl betaine, sodium cocoyl sarcosinate, disodium oleamido MIPA sulfosuccinate, disodium cocamido MIPA sulfosuccinate, disodium laureth sulfosuccinate, cocoamphocarboxy-glycinate, disodium oleamido MEA sulfosuccinate, amine glycinates, amine propionates and amine sultaines, and mixtures thereof. Preferably, a mixture of two or more different surfactants, in particular sodium laureth sulfate and sodium cocoyl sarcosinate; or sodium laureth sulfate and disodium laureth sulfosuccinate; or sodium lauryl sulfate, sodium laureth sulfate, TEA lauryl sulfate and cocamidopropyl betaine, may be used in the present shampoos. In the shampoos according to the present invention, the total amount of surfactants may range from about 36% to about 55% (w/w). Preferably, the weight of amphoteric surfactants is less than 15 % by weight of the total amount of surfactants.

In the above definitions, and hereinafter, the term 'MEA' signifies a mono-ethanolamide of formula RCO-NH-$CH_2CH_2$-OH, the term 'DEA' signifies di-ethanol amide of formula RCO-N($CH_2CH_2$-OH)$_2$, 'TEA' signifies triethanolammonium ; the term 'MIPA' signifies a mono-isopropanol amide of formula

$RCO\text{-}NH\text{-}CH_2\text{-}CHOH\text{-}CH_3$ ; wherein each RCO-group is a fatty acid residue, such as a C13-19alkylcarbonyl or C13-19alkenylcarbonyl group.

Suitable foaming agents (foam boosters and stabilizers) for use in the shampoos according to the present invention may be selected from the group of fatty acid mono- and dialkanol-amides comprising cocamide MEA, cocamide DEA, oleamide MEA, oleamide DEA and mixtures thereof. The foaming agent may be present in a range from about 1 to about 10 % (w/w), preferably from about 2 to about 6 % (w/w), in particular about 4 to about 5 % (w/w). These ingredients typically also have a thickening effect on the formulation.

Suitable preservatives for use in the present shampoos are dermatologically acceptable preservatives, e.g. tetrasodium or disodium EDTA, methylparaben, propylparaben, butylparaben, ethylparaben, imidazolidinyl urea, phenoxyethanol, quaternium 15, citric acid, preferably in combinations with one another. Tetrasodium and disodium EDTA, and citric acid also function as chelating agents.

As disclosed in US-5,456,851, when the concentration of ketoconazole, or for that matter that of any other antifungal, is at the lower end of the ranges mentioned hereinabove, the addition of a carefully controlled amount of an antioxidant selected from the group consisting of butylated hydroxytoluene ("BHT"), butylated hydroxy-anisole ("BHA"), ascorbic acid and N-acetyl-cysteine effectively stabilizes the ketoconazole or other azole present in the shampoo against degradation during accelerated aging for 13 weeks at 50°C, which is considered to be predictive of performance during storage at ambient temperatures for two years. Effective stability is considered to be a loss of active ingredient during storage of not more than about 10 percent. The proportion of BHT or BHA that has been found to be most effective is within the range of from about 0.01 % to about 1 % (w/w). Proportions greater than this amount do not stabilize ketoconazole as effectively for the 13-week accelerated aging period, although if one extends the accelerated aging period longer than 13 weeks, greater proportions of BHT or BHA tend to be more effective, since the BHT or BHA itself is also subject to degradation. However, it is well recognized by government regulatory agencies and in the pharmaceutical and cosmetic industries that stability testing for 13 weeks at 50°C is quite sufficient to predict product stability during normal shelf life storage for two (2) years at room temperature. It is also equally important that, for safety reasons (that is, to minimize the potential for skin sensitization), it is desired to use as small an amount as possible of BHT or BHA.

Since shampoo users expect a shampoo to be slightly viscous, one or more thickeners are often included in the formulation which give it a viscosity in the range of 4,000 to 9,000 mPa.s at room temperature. A suitable thickener is a carbomer or polycarboxylic acid, such as Carbopol ™ 1342 or Carbopol ™ 1382, which is thickened by the addition of sodium hydroxide or sodium chloride at the end of the preparation. Other suitable thickeners are the foaming agents mentioned hereinabove, preferably cocamide MEA.

The shampoo may further comprise one or more pearlizing agents selected from the group consisting of ethylene glycol distearate, ethylene glycol monostearate and mixtures thereof, at a concentration of 0.0% to 2 % ; one or more plant extracts, e.g. from aloe, arnica, birch, bladder wrack, gentian, ginseng, hamamelis (witch hazel), hawthorn, kina, lemon, nasturtium, rosemary, tea tree and the like, at a concentration of from 0.0% to 5% ; vitamins such as, for example, vitamin E (tocopherol) and derivatives, e.g. tocopheryl acetate, panthenol, and the like, at a concentration of 0.0% to 3%; antiinflammatory products of synthetic or natural origin, e.g. bisabolol, at a concentration of 0% to 5% ; fragrances at a concentration of 0% to 2%; and one or more colorants.

The shampoo may further comprise from 0.0 % to 10 % of a conditioner such as polyquaternium-7, polyquaternium-10 or a similar cationic quaternary polymer, e.g. a quaternary silicone polymer. Also suitable are other silicone compounds such as polyalkyl siloxanes, polyalkyl arylsiloxanes, polyether siloxane copolymers and mixtures thereof. Polyalkyl siloxanes useful herein include, for example, poly-dimethylsiloxanes (PDMS). Polyalkylaryl siloxanes that may be used include polymethylphenylsiloxanes. Polyether siloxane copolymers that may be used include polypropyleneoxide modified polydimethylsiloxanes. Ethylene oxide or mixtures of ethylene oxide and propylene oxide may also be used. The water insoluble ones are preferred. Gums of the above described siloxane polymers are most desirable for use herein. These siloxane polymer gums are rigid as opposed to a liquid or fluid, with high mass molecular weights of from about 200,000 to about 1,000,000 and viscosities from about 100,000 mPa.s to about 150,000,000 mPa.s at 25 °C. Polydimethyl siloxane gums are preferred. These gums have a viscosity of from about 100,000 mPa.s to about 150,000,000 mPa.s at 25 °C. The gums selected for use herein have a viscosity such that when blended with a PDMS fluid the viscosity of the blend of gum and fluid falls within this range. Such PDMS fluids are used at levels from about 50% to about

60% of the total weight of said gum-fluid blend. Most preferred for the present invention is a blend containing from about 40% to about 60% PDMS fluid and from about 60% to about 40% PDMS gum. The preferred PDMS fluid is dimethicone fluid which has a viscosity of about 350 mPa.s at 25 °C.

The pH of the shampoos according to the present invention are conveniently established using dermatologically acceptable acids, bases and buffers. The pH can range from about 4 to about 10, but preferably is in the range of about 6.5 to about 8, in particular from about 6.9 to about 7.4.

Some of the first active ingredients when at approximately neutral pH (pH 6 to 8), have limited solubility. In order to keep these agents homogeneously distributed throughout the shampoo, a suspending agent such as, for example, Avicel RC-591™ (a mixture of sodium CMC and microcrystalline cellulose) may be added. Several of the shampoo base ingredients, however, have considerable suspending properties of their own, and therefore the inclusion of particular suspending agents in the present shampoos is entirely optional.

The components of the shampoo are employed in conventional amounts, for example:

(a) 36% to 55% surfactants,
(b) 2% to 6% foaming agent,
(c) 0.1% to 2% antifungal,
(d) 0.05 to 2 % phospholipid
(e) 0.2% to 1.3 % thickener,
(f) 0.01% to 1% BHT or BHA;
(g) preservatives sufficient to retard degradation of the final composition in order to give adequate shelf life,
(h) acid, base or buffer to yield a pH in the desired range, and
(i) water qs ad 100% (that is, sufficient water to make 100%).

Examples

In the following, a general process for preparing shampoos according to the present invention is presented. Suitable amounts for each of the ingredients can be derived from the preceding description and from the exemplary formulations shown in the tables hereinafter.

A vessel was charged with a 1.64% stock solution of Carbopol 1342 (prepared using a Quadro disperser which functions by keeping the powdered polymer evenly divided and

pulling the powder by a vacuum into a stream of water) and deionized water, and heated to about 70°C. Both surfactants, i.e. sodium laureth sulfate and sodium cocoyl sarcosinate, were added, followed by the foaming agent, cocamide MEA, and a pearlizing agent (ethylene glycol distearate) and mixed until complete dissolution. Then the BHT was added and the mixture was stirred until complete dissolution thereof. The solution was allowed to cool slightly, whereupon the antifungal ingredient was added while stirring well. (The antifungal is added while the pH is slightly acidic, to facilitate dissolution.) Next, the phospholipid was dispersed into the mixture and stirred until homogenously dispersed. The mixture was allowed to cool to about 40°C, at which temperature there were added the conditioner (polyquaternium-7), the preservatives quaternium-15 and tetrasodium EDTA, the colorants and fragrances, and the NaCl for thickening the solution. The pH of the solution was adjusted to 6.9-7.4 with a 25% aq. solution of NaOH and deionized water was added to the final volume. Similar shampoo formulations can prepared using analogous processes which will be apparent to the person skilled in the art.

Using the general procedures described above, the following shampoo formulations according to the present invention can be made ; all quantities hereinafter are parts by weight.

The formulations according to the present invention are useful in the treatment of disorders such as dandruff, seborrheic dermatitis, the control of psoriasis, the reduction of oil or sebum production of the scalp, and the like disorders and discomforts. The formulations are to be applied topically to the affected body parts at regular intervals, in particular from at least once weekly to about once daily. Preferably they are employed more often in the beginning of the treatment, e.g. from 4 to 7 times a week, and less frequently in a later stage when the desired effect has been obtained and relapse is to be prevented (e.g. once or twice a week).

Example 1: Shampoo formulations for normal hair (with conditioner)

| *Ingredients* | *(a)* | *(b)* |
|---|---|---|
| sodium laureth sulfate | 30 | 30 |
| sodium cocoyl sarcosinate | 10 | 10 |
| cocamide MEA | 4 | 4 |
| ketoconazole USP | 0.5 | 1 |
| Phospholipid PTC | 0.5 | 1 |
| glycol distearate | 1.25 | 1.25 |
| polyquaternium-7 | 1 | 1 |
| Carbopol™1342 | 0.6 | 0.6 |
| tetrasodium EDTA | 0.5 | 0.5 |
| perfume oil | 0.5 | 0.5 |
| sodium chloride | 0.3 | 0.3 |
| sodium hydroxide 25% | 0.92 | 0.9 |
| butylated hydroxytoluene | 0.1 | 0.1 |
| quaternium-15 | 0.05 | 0.05 |
| colorants | 0.001 | 0.001 |
| deionized water qs ad | 100 | 100 |

Example 2: Shampoo formulations for oily hair (with conditioner)

| *Ingredients* | *(a)* | *(b)* | *(c)* |
|---|---|---|---|
| sodium laureth sulfate | 33.33 | 33.33 | 33.33 |
| sodium cocoyl sarcosinate | 11 | 11 | 11 |
| cocamide MEA | 4 | 4 | 4 |
| ketoconazole USP | 0.5 | 0.75 | 1.2 |
| Phospholipid PTC | 0.5 | 0.25 | 0.8 |
| glycol distearate | 1.25 | 1.25 | 1.25 |
| polyquaternium-7 | 0.6 | 0.6 | 0.6 |
| Carbopol™ 1342 | 0.75 | 0.75 | 0.75 |
| tetrasodium EDTA | 0.5 | 0.5 | 0.5 |
| perfume oil | 0.5 | 0.5 | 0.5 |
| sodium chloride | 0.3 | 0.3 | 0.3 |
| sodium hydroxide 25% | 1.18 | 1.243 | 1.18 |
| butylated hydroxytoluene | 0.1 | 0.1 | 0.1 |
| quaternium-15 | 0.05 | 0.05 | 0.05 |
| colorants | 0.0053 | 0.0053 | 0.0053 |
| deionized water qs ad | 100 | 100 | 100 |

Example 3: Shampoo formulations for dry or damaged hair (with conditioner)

| *Ingredients* | *(a)* | *(b)* | *(c)* |
|---|---|---|---|
| sodium laureth sulfate | 30 | 30 | 30 |
| sodium cocoyl sarcosinate | 10 | 10 | 10 |
| cocamide MEA | 4 | 4 | 4 |
| ketoconazole USP | 0.75 | 0.33 | 1 |
| Phospholipid PTC | 0.25 | 0.67 | 1 |
| glycol distearate | 1.25 | 1.25 | 1.25 |
| polyquaternium-7 | 5 | 5 | 5 |
| Carbopol™ 1342 | 0.5 | 0.5 | 0.5 |
| tetrasodium EDTA | 0.5 | 0.5 | 0.5 |
| perfume oil | 0.5 | 0.5 | 0.5 |
| sodium chloride | 0.4 | 0.4 | 0.3 |
| sodium hydroxide 25% | 0.7333 | 0.733 | 1.19 |
| butylated hydroxytoluene | 0.1 | 0.1 | 0.1 |
| quaternium-15 | 0.05 | 0.05 | 0.05 |
| colorants | 0.0018 | 0.0018 | 0.0018 |
| deionized water qs ad | 100 | 100 | 100 |

In all the formulations given above in Examples 1-3, the proportion of sodium hydroxide may vary slightly, to arrive at the preferred pH level of 6.9 to 7.4, and the proportion of salt (NaCl) may vary, to arrive at the desired viscosity. Formulations prepared according to the improved process and wherein the colorants have been omitted, have an off-white pearlescent look.

Example 4 : Combination of Phospholipid PTC and Ketoconazole (with conditioner)

| *Ingredients* | *Percent* |
|---|---|
| purified water | 44.30 |
| sodium laureth sulfate | 15.00 |
| sodium lauryl sulfate | 10.00 |
| TEA lauryl sulfate | 12.00 |
| Phospholipid PTC | 2.10 |
| ketoconazole | 1.00 |
| methylparaben | 0.20 |
| propylparaben | 0.05 |
| cocamide MEA | 5.00 |

| | |
|---|---|
| ethylene glycol distearate | 1.25 |
| polyquaternium-7 | 3.00 |
| imidazolidinyl urea | 0.50 |
| cocamidopropyl betaine | 5.00 |
| citric acid | 0.35 |
| fragrance | 0.25 |
| | 100.00 |

Example 5 : Combination of Phospholipid PTC and Elubiol (with conditioner)

| *Ingredients* | *Percent* |
|---|---|
| purified water | 44.30 |
| sodium laureth sulfate | 15.00 |
| sodium lauryl sulfate | 10.00 |
| TEA lauryl sulfate | 12.00 |
| Phospholipid PTC | 2.10 |
| elubiol | 1.00 |
| methylparaben | 0.20 |
| propylparaben | 0.05 |
| cocamide MEA | 5.00 |
| ethylene glycol distearate | 1.25 |
| polyquaternium-7 | 3.00 |
| imidazolidinyl urea | 0.50 |
| cocamidopropyl betaine | 5.00 |
| citric acid | 0.35 |
| fragrance | 0.25 |
| | 100.00 |

In the formulations given above in Examples 4 and 5, the proportion of citric acid may vary slightly, to arrive at the preferred pH level of 6.9 to 7.4. The formulations were prepared according to the improved process and have an white-pearlescent look.

Example 6 : Ketoconazole (2.1 %) and Phospholipid PTC 2% and 1 % (w/w) shampoos (without conditioner)

| | | |
|---|---|---|
| ketoconazole | 2.100 g | 2.100 g |
| Phospholipid PTC | 2.000 g | 1.000 g |
| imidazolidinyl urea | 0.200 g | 0.200 g |
| disodium laureth sulfosuccinate | 15.000 g | 15.000 g |

| | | |
|---|---|---|
| cocamide DEA | 2.000 g | 2.000 g |
| hydrolized laurdimonium | 1.000 g | 1.000 g |
| macrogol 120 | 1.000 g | 1.000 g |
| perfume | 0.200 g | 0.200 g |
| hydrocloric acid | 0.400 g | 0.400 g |
| red erythrosine (FD & C No. 40) | 0.002 g | 0.002 g |
| sodium laureth sulfate | 38.000 g | 38.000 g |
| sodium hydroxide | 0.100 g | 0.100 g |
| sodium chloride | 0.500 g | 0.500 g |
| purified water | q.s. ad 100 g | q.s. ad 100 g |

Example 7 :

In vitro synergisitic inhibitory effects between ketoconazole and Phospholipid PTC against Malassezia furfur

Checkerboard interaction experiments involving nine isolates of Malassezia furfur (M. furfur) and the test substances with doubling dilution steps showed the combination of test substances to be highly synergistic.

Ketoconazole was dissolved in DMSO to give a stock solution containing 2000 µg/ml. Phospholipid PTC was diluted with ethanol to give a stock solution containing 2000 µg/ml. A series of six further 3.162-fold dilutions of each substances was prepared in the same solvent (This dilution factor = SQRT(10), so that every second dilution was therefore a 10-fold dilution). Each of the seven concentrations of test substance was then further diluted in water to 12 times the final test concentration. An 8x8 checkerboard array of dilutions was next prepared in the wells of flat-bottomed, plastic microdilution plates with the ketoconazole dilution series arranged vertically and the dilutions of Phospholipid PTC arranged horizontally. Each well contained 10 µl of solution of each test substance. In an extra column of microdilution wells, 10 µl volumes of matching aqueous dilutions of the solvents alone were pipetted, to provide compound-free controls.

The panel of 9 M. furfur isolates used in the study was obtained from the fungal stock collection of the Department of Bacteriology and Mycology at the Janssen Research Foundation. All of the isolates were originally isolated from clinical material and three of them had been freshly isolated within 9 months prior to the study. The yeasts were maintained by subculture on a modification of the medium called "H. Dixon's formulation" by Van Abbe, N.J. (1964) [The investigation of dandruff. J. Soc. Cosmetic

Chemists 15, 609-630]. This medium contained (per 1000 ml water) : malt extract (Difco) 36 g; Mycological peptone (Oxoid) 6 g; Bacto-oxgall (Difco) 20 g; Tween 40 (Merck) 10 ml; glycerol (Difco) 2.5 ml; and Bacto-agar (Difco) 20 g. For use as a broth formulation the agar was omitted. Agar-based and broth versions of the medium were autoclaved for 5 min at 100 °C.

Experimental inocula were prepared by incubation for 2 days at 30 °C in Dixon broth maintained in constant rotation at 20 rpm in test tubes angled at 5° from the horizontal. The broth cultures were standardized spectrophotometrically so they all gave an OD reading of 1.0 at 530 nm. These suspensions contained an average of 2x106 cells/ml as measured in agar plate counts. The yeasts were diluted 500-fold into Dixon broth to give suspensions containing 3-10x105 CFU/ml.

The inoculated medium was added in 100 µl volumes to the microdilution wells already containing dilutions of the test substances. The plates were sealed with adhesive stickers and incubated for 5 days at 30 °C. The stickers were then removed and growth turbidity measured with the aid of a microplate reader as absorbance at 490 nm. For each combination of test substances nine microplates were run in parallel, each inoculated with a different M. furfur isolate. A tenth plate was set up inoculated with Dixon broth only, to provide negative control OD readings.

With the aid of a computer spreadsheet template, the OD490 of each microplate well containing combinations of test substances, corrected for absorbance measured in the negative control plate, was expressed as a percentage of the mean OD490 of the eight test substance-free positive control wells inoculated with M. furfur. The results were expressed in an 8x8 matrix and automatically shaded to indicate growth inhibition at or below 25% of control. In this way an indifferent interaction between two test substances would appear as a dark rectangle at the bottom right of the graphic, a synergistic interaction would appear as an inverted "L" shape at the bottom right of the graphic and an antagonistic interaction would appear as an extension of the rectangle towards the top left of the graphic. From the checkerboard results, minimal inhibitory concentrations (MIC) were determined as the lowest concentrations of test compounds, alone and in combination with other compounds, and fractional inhibitory concentrations (FIC) were calculated for each compound by the formula:

MIC(compound alone)/MIC(compound in presence of second compound)

The sum of the two FICs then gave a result of 1.0 for compounds with no interactive

effect (indifference), <1.0 for compounds with a synergistic interaction and >1.0 for compounds with an antagonistic interaction.

Clearly positive results indicative of possible synergy were obtained with Phospholipid PTC. The sum of the fractional inhibitory concentrations (FIC) for the combination ketoconazole and Phospholipid PTC against 9 M. furfur isolates in vitro was :

| M. furfur isolate no. | FIC |
|---|---|
| B 39387 | 0.63 |
| B 45836 | 0.63 |
| B 45838 | 0.63 |
| B 58047 | 0.13 |
| B 58200 | 0.63 |
| B 58968 | 0.63 |
| J95-0821 | 0.13 |
| J95-0822 | 1 |
| J95-1435 | 1 |

The degree of synergy extended well beyond one-dilution effects that could have arisen by chance. The activity of Phospholipid PTC in combination with ketoconazole was therefore further investigated against the test panel of nine isolates, but with smaller (two-fold) dilution steps in the concentration series. The sum of the fractional inhibitory concentrations (FIC) for the combination ketoconazole and Phospholipid PTC against 9 M. furfur isolates in vitro was :

| M. furfur isolate no. | FIC |
|---|---|
| B 39387 | 0.38 |
| B 45836 | 0.38 |
| B 45838 | 0.16 |
| B 58047 | 0.38 |
| B 58200 | 0.19 |
| B 58968 | 0.38 |
| J95-0821 | 0.38 |
| J95-0822 | 0.75 |
| J95-1435 | 0.38 |

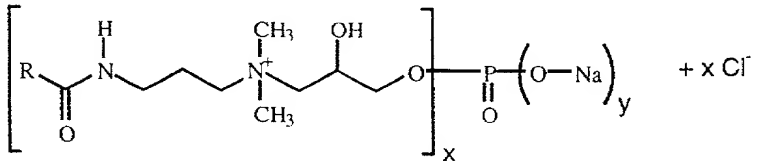
The results confirm unequivocally that both test compounds indeed interact synergistically with ketoconazole against M. furfur in vitro.

Claims

1. A body or hair cleansing composition comprising
   (a-1) one or more antifungals inhibiting fungal ergosterol biosynthesis as a first active ingredient,
   (a-2) a synthetic amphotheric phospholipid as a second active ingredient, and
   (b) art-known body or hair cleansing product ingredients as a carrier.

2. A composition according to claim 1 wherein the antifungal inhibiting fungal ergosterol biosynthesis is an azole selected from the group comprising ketoconazole, econazole, elubiol, miconazole, itraconazole, fluconazole, or a mixture thereof, or is an allylamine selected from the group comprising terbinafine, naftifine, or a mixture thereof.

3. A composition according to claim 2 wherein the phospholipid has the formula




wherein R represents a straight, saturated, mono-unsaturated or poly-unsaturated C7-19 alkyl group ; x represents 1, 2 or 3 and x + y = 3 ; and mixtures thereof.

4. A composition according to claim 1, 2 or 3 wherein the first and the second active ingredients are present in quantities producing a mutual synergistic effect on the inhibition of the growth of Malassezia furfur.

5. A composition according to any one of the preceding claims wherein the first active ingredient is present in an amount ranging from about 0.1 % to about 2 % (w/w) and the second active ingredient is present in an amount ranging from about 0.04 % to about 10 % (w/w), the amount of the latter being expressed as weight of phospholipid.

6. A composition according to any one of the preceding claims formulated as a shampoo.

7. A shampoo according to claim 6 wherein the art-known shampoo ingredients comprise one or more of a surfactant, a foaming agent, a thickener sufficient to give the final formulation a viscosity in the range of 4,000 to 9,000 mPa.s at room temperature, a preservative, an anti-oxidant, and acid or base or buffer sufficient to give the shampoo a pH in the range of from about 4 to about 10.

8. A shampoo according to claim 7 comprising one or more surfactants selected from the group comprising sodium C14-16 olefin sulfonates, sodium lauryl sulfate, sodium laureth sulfate, cocamidopropylamine oxide, lauryl amine oxide, lauramido DEA, cocamidopropyl betaine, lauryl dimethyl betaine, cocodimethyl sulphopropyl betaine, sodium cocoyl sarcosinate, disodium oleamido MIPA sulfosuccinate, disodium cocamido MIPA sulfosuccinate, disodium laureth sulfosuccinate, cocoamphocarboxyglycinate, disodium oleamido MEA sulfosuccinate, amine glycinates, amine propionates and amine sultaines, and mixtures thereof.

9. A shampoo according to claim 7 wherein the foaming agent is selected from the group of fatty acid mono- and di- alkanolamides consisting of cocamide MEA, cocamide DEA, oleamide MEA, oleamide DEA and mixtures thereof.

10. A shampoo according to claim 7 wherein the antioxidant is butylated hydroxytoluene or butylated hydroxyanisole employed in an amount of about 0.01 to about 1 % (w/w).

11. A shampoo according to claim 7 further comprising a conditioner.

12. A shampoo according to claim 7 further comprising one or more pearlizing agents selected from the group consisting of ethylene glycol distearate, ethylene glycol monostearate and mixtures thereof.

13. A shampoo according to claim 7 further comprising one or more fragrances and one or more colorants.

14. A process for preparing a shampoo formulation as defined in any one of the preceding claims comprising the steps of :

(a) heating a solution of thickener and deionized water,

(b) mixing the surfactants, the foaming agent and optionally the pearlizing agent with the solution of (a),

(c) mixing the BHT with the solution of (b),

(d) mixing the antifungal with the solution of (c),

(e) dispersing the phospholipid in the mixture of (d),

(f) allowing the suspension of (e) to cool somewhat and mixing therewith the preservative(s), the sodium chloride for thickening to the required viscosity, and optionally the conditioner, the fragrance(s) and colorant(s),

(g) adding acid, base or buffer to the solution of (f) to yield a pH in the range of 4 to 10, and

(h) adding deionized water to the solution of (g) to 100%.

**COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY**
(Includes Reference to PCT International Applications) PCT/EP98/02143

ATTORNEY S DOCKET NUMBER
JAB 1267-PCT-US

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Compositions containing an antifungal and a phospholipid

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/EP98/02143

on April 07, 1998

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowlege the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

**PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:**

| COUNTRY (if PCT indicate PCT) | APPLICATION NUMBER | DATE OF FILING (day month year) | PRIORITY CLAIMED UNDER 35 USC 119 |
|---|---|---|---|
| E.P. | 97.201.101.9 | 14 April 1997 | ☒ YES ☐ NO |
| | | | ☐ YES ☐ NO |
| | | | ☐ YES ☐ NO |
| | | | ☐ YES ☐ NO |
| | | | ☐ YES ☐ NO |



(January 1991)

**Combined Declaration For Patent Application and Power of Attorney (Continued)**
(Includes Reference to PCT International Applications) PCT/EP98/02143

ATTORNEY'S DOCKET NUMBER: JAB 1267-PCT-US

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowlege the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

**PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:**

| U S APPLICATIONS | | STATUS (Check one) | | |
|---|---|---|---|---|
| U S APPLICATION NUMBER | U S FILING DATE | PATENTED | PENDING | ABANDONED |
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| PCT APPLICATIONS DESIGNATING THE U S | | | | | |
|---|---|---|---|---|---|
| PCT APPLICATION NO | PCT FILING DATE | U S SERIAL NUMBERS ASSIGNED (if any) | | | |
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**POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.** *(List name and registration number)*

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

| SIGNATURE OF INVENTOR 201 | SIGNATURE OF INVENTOR 202 | SIGNATURE OF INVENTOR 203 |
|---|---|---|
| DATE: April 23, 1999 | DATE: April 23, 1999 | DATE: April 23, 1999 |